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PERLEGEN SCIENCES, INC.
LEGAL DEPARTMENT
2021 STIERLIN COURT
MOUNTAIN VIEW, CA 94043

EXAMINER	
WHALEY, PABLO S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/768,788	BERNO ET AL.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-118 and 133-139* is/are pending in the application.

4a) Of the above claim(s) *50,51,53,55-63,116,117 and 119-132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-49,52,54,64-115,118 and 133-139* is/are rejected.

7)☒ Claim(s) *29-32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/24/05; 5/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

APPLICANT'S ELECTION

Applicant's election with traverse of Group I (Claims 1-118 and 133-139) in the reply filed on 03/24/2006 is acknowledged. The traversal is on the basis that examination of Groups I and II would not create an undue search burden if searched together since there was no clear indication of separate classification or separate status in the art. This is not found persuasive because the examiner maintains that the Groups are distinct for the reasons previously set forth and would therefore require a separate search. In addition, the examination process requires a search of non-patent literature, U.S. patent publications, U.S. patents, as well as foreign patent literature. The requirement is still deemed proper and is therefore made FINAL.

Applicant's election with traverse of Specie A (drawn to resistance or susceptibility or adverse reaction to a therapy, as recited in instant claim 10), Specie B (drawn to intensities determined by signal averaging using at least two intensity of signal measurements, as recited in instant claim 52), Specie C (drawn to mean intensities based on trimmed means, as recited in instant claims 54, 111, and 117), Specie D (drawn to candidate genes not previously known, as recited in instant claims 129 and 131), Specie E (drawn to nucleotide segment positions proximal to a region of a candidate gene, as recited in instant claims 129-132) is acknowledged. The restriction requirement for Specie A is hereby withdrawn as it is no longer deemed to be a search burden. The traversal is on the basis that examination of Species D and E would not create an undue search burden if searched together since the recited candidate genes are not mutually exclusive. This is not found persuasive because the examiner maintains that the species of Specie D and E are distinct for the reasons previously set forth and would therefore

require separate sequence searches. Furthermore, the arguments are moot in light of the fact that Specie D and E are drawn to a non-elected invention.

Claims 50, 51, 53, 55-63, 116, 117, and 119-132 are hereby withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/24/2006.

CLAIMS UNDER EXAMINATION

Claims 1-49, 52, 54, 64-115, 118 and 133-139 are herein under examination as the read on the following elected species:

- Specie B (drawn to intensities determined by signal averaging using at least two intensity of signal measurements), as recited in instant claim 52.
- Specie C (drawn to mean intensities based on trimmed means), as recited in instant claims 54, 111, and 117.

INFORMATION DISCLOSURE STATEMENT

The information disclosure statements filed 1/24/05 and 5/10/04 have been considered in full.

OBJECTIONS

Claims 29-32 are objected to because of the following informalities: Claims 29-32 are grammatically incorrect, and should recite "probes per square centimeter." Appropriate correction is required.

CLAIM REJECTIONS - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-49, 52, 54, 64-115, and 118 are rejected under 35 U.S.C. 101 because these claims are drawn to non-statutory subject matter. Claims 1, 108, and 118 are directed to computer-implemented methods for characterizing an interrogation position in a nucleic acid segments which do not recite either a physical transformation of matter nor a practical application. Claims 1, 108, and 118 recite steps drawn to "inputting" allele frequency measures (i.e. data) into a computer system and analyzing data in the computer system. While "inputting" may be a physical step, the claimed method as a whole does not result in a physical transformation of matter. It is noted that computer implemented processes may be statutory where they recite a concrete, tangible, and useful result (i.e. a practical application). However, no actual, concrete result is recited in the claims, nor is any useful result "produced" in a tangible form useful to one skilled in the art. For these reasons, the claims are not statutory.

Claims 138-139 are directed to a computer-readable medium holding computer readable code for characterizing a position in a nucleic acid segment. Computer readable code (i.e. non-functional descriptive material) stored on a computer-readable medium is not statutory subject matter, as the medium may be an electromagnetic carrier wave which is not necessarily a physical object. For the reasons set forth above, the claims are not statutory. For an updated discussion of statutory considerations with regard to non-functional descriptive material and

computer-related inventions, see the Guidelines for Patent Eligible Subject Matter at 1300 OG 142, Annex IV, Nov. 22, 2005.

LACK OF UTILITY

Claims 1-5, 17-49, 52, 54, 64-74, 77, 108-115, 118, 133, and 138 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a well-asserted utility or a well-established utility.

In the instant case, the claimed invention is not supported by a well-established or a specific, substantial and credible asserted utility. The instant claims recite a general method of "characterizing an interrogation position" in a nucleic acid segment which does not have a well-established utility. The specification discloses instances where the instant invention may be "useful", such as analyzing data from nucleic acid arrays to characterize SNPs [0009] and [0043]. However, the instant claims do not recite SNPs therefore this asserted utility is not specific to the instant claims. For these reasons, the claimed subject matter does not have a specific, substantial, and credible utility.

Claims 1-5, 17-49, 52, 54, 64-74, 77, 108-115, 118, 133, and 138 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 68, 70-71, 77, 79, 84-85, 89-93, 99-100, and 138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 68 recites the limitations "a further first measure" and "a further second measure." It is unclear as to the intended meaning of a "further first measure" and "further second measure" as the term "further" could be interpreted as a distance, an alternate measurement, or something else. Clarification is requested.

Claim 70 recites the limitation "the first equation is constrained by a second equation." It is unclear in what way the second equation recited in instant claim 70 "constrains" the first equation recited in parent claim 69. Clarification is requested.

Claims 84 and 99 recite the limitation "a further plurality." It is unclear as to the intended meaning of a "further plurality" as the term "further" could be interpreted as a distance, an alternate measurement, or something else. Clarification is requested.

Claim 92 recites the limitation "using an equation of the form $N_1 + N_2 - 2$." As parent claim 89 does not recite or define N_1 and N_2, it is unclear as to the intended meaning of these variables in this context. Clarification is requested. It is noted that claim 91 does recite an equation with N_1 and N_2 and defines these variable as well.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 10, 11, 14, 15, 17-21, 29-31, 33-36, 40, 41-43, 47, 48-52, 75, 108, and 109, 111-114, and 133-139 are rejected under 35 U.S.C. 103(a) as being made obvious by Fan et al. (Genome Research, 2000, Vol. 10, p.853-860), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kellam et al. (Antimicrobial Agents and Chemotherapy, 1994, Vol. 38, No. 1, p. 23-30).

Fan et al. a method for genotyping SNPs using generic high-density oligonucleotide arrays that contain thousands of 20-mer oligonucleotide tags [Abstract]. More specifically, Fan et al. teach the following aspects of the instant invention:

- Measurement and analysis of first, second, and third measurements of relative allele fractions (i.e. frequency) based on hybridization results from 44 individuals at two distinct

SNP positions [Fig. 3 and Abstract], which is a teaching for the first and second measures as in instant claim 1.

- Genotyping of 44 individuals for 142 human SNPs previously identified in hypertension candidates (i.e. phenotypic characteristic of interest) [Abstract] using perfect match (PM) probe data and mismatch (MM) control probe data [p.853, Col. 2, ¶ 2], which correlates to human case and control groups as in instant claims 2-6 and 11.
- Cluster analysis of hybridization results of 44 individuals (i.e. 10-100,000) at two SNP markers [Fig. 3], as in instant claims 6, 14, and 15.
- Allele frequency estimation for observed (i.e. unknown) versus known data based on SNPs at the interrogation position using a reference allele "C" [Fig. 5], as in instant claim 16.
- DNA data pooled in equal amounts from three groups [Fig. 5], as in instant claims 17-19.
- DNA label with detectable biotin-labeled markers [Fig. 1], as in instant claims 20-21.
- Fluorescent intensity signals from > 32,000 probe pairs based on quantification of relative allele fraction values (i.e. relative allele frequency) [Fig. 2], as in instant claim 28.
- Over 64,000 20-mer probes each occupying an area of 30 μm^2 [p.853, Col. 2, ¶ 2], which meets the limitation of instant claims 29-31 and 33-34.
- Fluorescent intensities are measured and corrected via background subtraction [p.854, Col. 1, ¶ 1 and Fig. 2], as in instant claims 35 and 36.
- Relative allele fraction values [Fig. 2(B)] and cluster analysis of hybridization results [Fig. 3], which are teachings for detection evaluation as in instant claim 39 and mismatch and perfectly complementary probes as in instant claim 40.

- Perfect match (PM) probes are paired with mismatch (MM) probes differing by a single base for hybridization-control [p.853, Col. 2, ¶ 2], which correlates to probes and reference probes with varying nucleotides as recited in instant claims 41, 42, and 47.
- Varying nucleotides at the interrogation position comprising A, C, and G [Table 1], as in instant claim 43.
- Observed versus known allele frequency estimation based on SNPs at the interrogation position using a reference allele "C" [Fig. 5], which is a teaching for the limitations of instant claim 48.
- Measurement of allele frequencies using PM and MM intensities (i.e. at least two intensity signals), as required by Specie B and recited in instant claims 52.
- Fluorescein and phycoerythrin hybridization signals (i.e. reference and alternate signals) [Fig. 2], as in instant claims 49, 50 and 52; relative allele fraction values (P) determined by calculating the log of total fluorescence intensity $(PM\text{-}MM)_{fluorescein}$ / [$(PM\text{-}MM)_{fluorescein}$ + $(PM\text{-}MM)_{phycoerythrin}$] [Fig. 2], which correlates to instant claims 49-52, 108, 109. It is noted that PM-MM intensity values are based on allele concentration [Fig. 4].
- Intensity data is corrected for background and spectral overlap [p.854, Col. 1, ¶ 1], as in instant claims 113 and 114.
- Exclusion of outliers from computed ranges of data sets [p.859, Col. 1, ¶ 1], as in instant claim 112.

Fan et al. does not specifically teach a computer-implemented method for inputting allele frequency data into a computer system, as in instant claims 1 and 133-139, phenotypic characteristic of interest directed to resistance to a therapy, as in instant claim 10, or a plurality of measures, as in instant claim 75.

Webster et al. teach computer-aided methods for analyzing nucleic acid hybridization intensities of probes sets at specific interrogation positions [0068] and monitoring gene expression [Abstract]. More specifically, Webster et al. teach the following aspects of the instantly claimed invention: In a computer system: inputting a plurality of hybridization intensities of pairs of perfect match and mismatch probes (i.e. first and second measures), as in instant claim 75, comparing (i.e. analyzing) the hybridization intensities of each pair of perfect match probes in order to generate a gene expression call of the sample nucleic acid sequence [Ref. Claim 13], which equates to steps of inputting and analyzing as in instant claim 1. Webster et al. further teach at least 2 intensity signal measurements for reference and alternate gene expression data [Fig. 8], as required by Specie B and recited in instant claims 52 and 108, and a computer system comprising a monitor, hard drive for storing and retrieving computer code for incorporating the invention, processor [0046] and [Fig. 2], and scanner [Fig. 3], as in instant claims 133-139.

Kellam et al. teach a rapid phenotypic assay for assessment of drug susceptibility of HIV isolates to reverse transcriptase inhibitors [Abstract]. More specifically, Kellam et al. teach the following aspects of the instantly claimed invention: phenotypic characteristic of interest is resistance to HIV treatment using therapeutic agent [Abstract, Tables 2 and 3], as recited in instant claim 10. It is noted that as Kellam et al. also provides a teaching for likelihood of resistance to infection, as in instant claim 7, as high resistance to a drug correlates to an increased likelihood for infection.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the rapid phenotypic assay taught by Kellam et al. and the computer-implemented analysis method of Webster et al. with the method for genotyping SNPs taught by Fan et al., where the motivation would have been to use a high throughput computer-

implemented method for genotypic and phenotypic analysis of disease [Webster et al.] with phenotypic assay better suited for complex resistance patterns in humans [Kellam et al.], resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method of Webster et al. and the rapid phenotypic assay taught by Kellam et al. with the method for genotyping SNPs taught by Fan et al. as Webster et al., Kellam et al., and Fan et al. all teach the genotypic and phenotypic analysis of data.

Claims 1, 3-6, 48, 52, 75, 77, 79, 80, 81, 83, 84, 86-90, 98, 99, 100, 103, 104, 108, 109, 111, 112, 113, 135, and 136 are rejected under 35 U.S.C. 103(a) as being made obvious by Germer et al. (Genome Research, 2000, Vol. 10, p.258-266), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-6).

Germer et al. teach a high-throughput method for determining the allele frequency of biallelic polymorphisms [Abstract]. More specifically, Germer et al. teach the following aspects of the instant invention:

- relative allele frequency measurements for two data sets using SNP sites and fractional predetermined threshold (C_t) representing [Fig. 1] and analysis of measurements [Table 1], as in instant claim 1;
- human and mouse DNA [Abstract], as in instant claims 3, 4, and 5;
- SNP markers functionally related to a disease (i.e. phenotypic characteristics of interest) [p.263, Col. 1, ¶ 2], as in instant claim 6;

- analysis at a plurality of interrogation positions [Fig. 4], as in instant claims 77, 98, and 99; calculation of mean, standard deviation , sampling errors (i.e. cutoff values based on standard deviation), [p.262, Col. 1] and frequency distribution (<15% and >85%) [p.261, Col. 2, ¶ 3], as in instant claims 79, 80, 86, 87-90;
- threshold value of 0.1 [Fig. 1], as in instant claim 83; Calculation of allele frequency at two alleles based on difference values (ΔC) and thresholds (C_t) [Fig. 1and Equation (1)], as in instant claim 100;
- accuracy of allele frequency measurement (i.e. validation) determined by genotyping and allele frequency [Fig. 3], as in instant claims 103 and 104;
- determining relative allele frequencies for multiple polymorphisms and comparing measured and known allele frequencies (i.e. reference and alternate) [Table 2] where frequencies represent the average of intensity values [p.261, Col. 2, ¶ 2], as in instant claims 48, 52 (as required by Species B), and 108; measurements made from matched and mismatched probes [p.259, Col. 1, ¶ 2], as in instant claim 109;
- Data has been corrected for differential amplification [Table 1], as in instant claim 113.
- Input/output files comprising ASCII files prepared using an editor (i.e. another data storage device), interactive user prompt (i.e. imaging device) [p.410, Col. 1, ¶ 3], as in instant claims 135 and 136.

Germer et al. do not specifically teach a computer-implemented method for inputting allele frequency data into a computer system, as in instant claims 1, 75, and 80, 81, and 84, or trimmed means, as required by Specie C (instant claims 54 and 111).

Webster et al. teach computer-aided methods for analyzing nucleic acid hybridization intensities indicating affinity between hybridization probes and sample nucleic acid sequences,

and monitoring gene expression [Abstract], as set forth above. More specifically, Webster et al. teach the following aspects of the instantly claimed invention: In a computer system: inputting a plurality of hybridization intensities of pairs of perfect match and mismatch probes (i.e. first and second measures), comparing (i.e. analyzing) the hybridization intensities of each pair of perfect match probes [Ref. Claim 13] based on difference and ratio thresholds [Ref. Claims 14 and 15], as in instant claims 1, 75, and 80, 81, and 84. Webster et al. further teach mean hybridization intensities of photon counts recorded from a cell (i.e. at least two instensity counts [0099], as required by Specie B and recited in instant claim 52; background subtraction and thresholding of intensity data [Fig. 11], as in instant claim 100, and reference and alternate gene expression data [Fig. 8], as in instant claim 108.

Kroll et al. teach robust methods for comparing measurements from gene expression data comprising normalization, mean, trimmed mean (i.e. outlier exclusion), and standard deviation [Abstract, Table 1, Table 2], as required by Specie C and recited in instant claims 54, 108, 111, and 112.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the trimmed mean method of Kroll el al. and the computer-implemented analysis method of Webster et al. with the high-throughput method for determining the allele frequency as taught by Germer et al., where the motivation would have been to use a more robust method for normalizing and comparing large data sets, as taught by Kroll et al. [Abstract], resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method of Webster et al. and using the trimmed mean method of Kroll et al. with the high-throughput method for determining the allele frequency of Germer et al. as all teach the analysis of gene expression data.

Claims 1-6, 11, 12, 13, 17-19, 22, 23, 26-28, 52, 64-68, 72, 75-77, and 133-139 are rejected under 35 U.S.C. 103(a) as being made obvious by Barcellos et al. (Am. J. Hum. Genet., 1997, Vol. 61, p.734-747), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-6).

Barcellos et al. teach a method using pooled DNA amplification of microsatelite markers to facilitate high-resolution genome screening for detection of disease loci by association [Abstract]. More specifically, Barcellos et al. teach the following aspects of the instant invention:

- DNA samples obtained from human patient samples (n=51) and control individuals (n=75) [p.735, Methods and Materials], which is a teaching for first and second samples as in instant claims 1-5, and 12. As humans are animals/mammals, claims 2-5 are anticipated.
- Estimation of allele frequencies in patients and controls [p.736, Col. 2, ¶ 2] and [Fig. 2], which is a teaching for first and second measures as in instant claim 1.
- Analysis of allele frequency data [p.737, Col. 2, ¶ 3 and Table 1], as in instant claim 1.
- Patients selected have hemochromatosis (i.e. phenotypic trait of interest) [p.735, Col. 2, ¶ 3], as in instant claims 6 and 10; and detection of disease-predisposing loci by association analysis [p.737, Col. 2, ¶ 1], which correlates to characterizing the interrogation position as being associated with the phenotypic characteristic of interest as in instant claim 6.
- Screening of 200 patients and 200 controls [p.741, col. 2, ¶ 1], which meets the limitation of instant claims 12 and 13.

- Pooling of patient and control DNA data and conversion to 2N allele-frequency counts for each pool size [p.736, Col. 2, ¶ 2] and labeling of samples with detectable marker as in instant claims 17-19.
- Use of pooled DNA amplification [Abstract], as in instant claim 22.
- Patient and control results using multiple oligonucleotide markers [Figs. 2, 3, and 4], as in instant claim 23.
- DNA samples obtained from mothers, fathers, and affected children and pooled separately for amplification and analysis [p.739, col. 1, ¶ 1], as in instant claim 26.
- Use of biallelic markers to calculate power for highly polymorphic microsatellites [p.740, Col. 2, ¶ 1 and ¶ 3], which correlates to biallelic polymorphisms as in instant claim 27.
- Peak height data (i.e. signal intensity) from genotyping profiles using a dinucleotide marker (i.e. a first probe on a two-nucleotide array) [Table 1] and a measure of allele frequency based on signal intensity [Table 2], as in instant claim 28.
- Association strength determined by absolute difference between patient and control allele frequencies [p.737, Col. 2, ¶ 1], as in instant claims 64, 72.
- Goodness of fit testing to measure the degree of closeness between allele-frequency distributions [p.737, Col. 1, ¶ 3] and association strength values of 0.20 (i.e. top 20%) and 0.5 (i.e. top 5%) [Table 2], as in instant claims 64-67.

Barcellos et al. do not specifically teach a computer-implemented method and apparatus for inputting allele frequency data into a computer system, as in instant claims 1, 52, 68, 75, and 133-139, signal averaging using at least two intensity of signal measurements as required by Specie B (instant claim 52), or trimmed means, as required by Specie C (instant claims 54 and 111).

Webster et al. teach computer-aided methods for inputting and analyzing nucleic acid hybridization intensities of probes sets at specific interrogation positions [0068] and monitoring gene expression [Abstract], as applied to claims 1, 52 (Specie B) 100, 108, and 133-139 above. Furthermore, Webster et al. teach the following aspects of the instantly claimed invention: allele frequency intensity blocks comprising a multitude of intensity patterns (i.e. further first and further second measures) at different interrogation positions [0071] [Fig. 7 and 8], as in instant claims 68, 75, 76, and 77.

Kroll et al. teach robust methods for comparing measurements from gene expression data comprising normalization, mean, trimmed mean (i.e. outlier exclusion), and standard deviation [Abstract, Table 1, Table 2], as required by Specie C and as in instant claims 54, 108, 111, and 112.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to combine the computer-implemented analysis method of Webster et al. and the trimmed mean technique of Kroll et al. with the high-resolution genome screening method taught by Barcellos et al., where the motivation would have been to use a high throughput computer-implemented method for genotypic and phenotypic analysis of disease [Webster et al.] resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method of Webster et al. and the high-resolution genome screening method of Barcellos et al. as both teach method of genomic analysis using allele frequency intensity data sets. One of skill in the art would have had a reasonable expectation of successfully using the trimmed means technique of Kroll et al. and the high-resolution genome screening method of Barcellos et al. as Barcellos et al. teach exclusion of data [Table 4] and statistical analysis of data.

Claims 78-83 are rejected under 35 U.S.C. 103(a) as being made obvious by Barcellos et al. (Am. J. Hum. Genet., 1997, Vol. 61, p.734-747), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-6), as applied to claims 1-6, 11, 12, 13, 17-19, 22, 23, 26-28, 52, 64-68, 72, 75-77, and 133-139, above, in further view of MathWorld (http://mathworld.wolfram.com/Pairedt-Test.html, © 1999 CRC Press LLC, p. 1-2) and The 2002 County Loan Rate Calculation Procedure (2002, p.1).

Barcellos et al., Webster et al., and Kroll et al. make obvious a computer-implemented method and system using pooled DNA amplification for genome screening, as set forth above.

Webster et al. further teach obtaining probe intensity values from a biological sample (i.e. common experimental condition) [0185], as in instant claim 78; calculating the mean values for intensity data obtained from experiments [Fig. 19], as in instant claims 52 (Specie B) and 80; and analyzing different based on user-defined thresholds [Fig. 19] [0145], which is a teaching for variable threshold values as in instant claims 81- 83.

Barcellos et al., Webster et al., and Kroll et al. do not teach a pair t-test or calculation of an Olympic Average, as in instant claims 78 and 79.

The MathWorld website teaches a method for determining the paired t-test, as in instant claim 79. The 2002 County Loan Rate Calculation Procedure teaches the calculation of Olympic Averages of data, as in instant claim 79.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to combine the computer-implemented method of Barcellos et al., Webster et al., and Kroll et al. with the data analysis methods as taught by MathWorld and The 2002 County Loan Rate Calculation Procedure, where the motivation would have been to remove outliers from the data set to improve the degree of closeness between allele-frequency

distributions [Barcellos et al., p.737, Col. 1, ¶ 3]. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method made obvious by Barcellos et al., Webster et al., and Kroll et al. and the Olympic Average and paired t-test as both Barcellos et al. and Webster et al. teach statistical analysis of data.

Claims 69, 72, 76, 77, 78, 81, and 84 rejected under 35 U.S.C. 103(a) as being made obvious by Barcellos et al. (Am. J. Hum. Genet., 1997, Vol. 61, p.734-747), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-6), as applied to claims 1-6, 11, 12, 13, 17-19, 22, 23, 26-28, 52, 64-68, 72, 75-77, and 133-139, above, and further in view of Excoffier et al. (Mol. Biol. Evol., 1995, Vol. 12, No. 5, p.921-927) and Walter et al. (Antimicrobial Agents and Chemotherapy, Jan. 2002, Vol. 46, No. 1, p.89-94).

Barcellos et al., Webster et al., and Kroll et al. make obvious a computer-implemented method and system using pooled DNA amplification for genome screening and the trimmed means technique, as set forth above.

Barcellos et al., Webster et al., and Kroll et al. do not teach the corrected allele frequency equations of instant claim 69.

Excoffier et al. teach a computer-implemented maximum-likelihood estimation algorithm for determining molecular haplotype frequencies [Abstract]. More specifically, Excoffier et al. teach the following aspects of the instant invention: generating estimated haplotype frequencies based on samples of 25 and 100 individuals and specific polymorphic positions [p.923, Col. 2, ¶ 2], computer analysis of actual haplotype frequency measurements (i.e. first measure) compared to estimated haplotype frequencies (i.e. second measure) [p.924, Col. 1, ¶ 2], as in instant claims

1, 2, 5, 6, and 118; phenotype frequencies based on *m* phenotypes and listed in summation notation as in instant claim 69 [p.922, Col. 1, ¶ 3, and Equation (3)]; calculating a different between first and second frequencies [p.924, Equation (10)], as in instant claim 72; iterative computation of successive haplotype frequencies [p.922, Col. 2, The EM Algorithm], as in instant claims 76 and 84; polymorphisms simulated using four allele positions [p.923, Col. 2, ¶, 2], as in instant claim 77; pairing measures of estimated and actual allele frequencies [p.924, Col. 1, ¶ 2], as in instant claim 78; calculation of mean values of data [Table 1], as in instant claim 80; estimated frequencies based on threshold values that vary between 1 and 0 [p.924, Col. 1, ¶ 3], as in instant claim 81.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the method maximum-likelihood frequency estimation algorithm taught by Excoffier et al. with the computer-implemented method and system using pooled DNA amplification for genome screening and the trimmed means technique made obvious by Barcellos et al., Webster et al., and Kroll et al., where the motivation would have been to provide an improved performance measure algorithm for predicting drug resistance in individuals [Walter et al., p.923, Col. 2, ¶ 4], resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully using the maximum-likelihood frequency estimation algorithm taught by Excoffier et al. with the computer-implemented method and system using pooled DNA amplification for genome screening and the trimmed means technique made obvious by Barcellos et al., Webster et al., and Kroll et al., as Excoffier et al. [p.927, Col. 1, ¶ 1] suggest their algorithm could be successfully applied to microsatellite data and used to identify haplotypes formed by the combination of microsatellite patterns, as taught by Barcellos et al., or haplotype data derived from oligotyping techniques or seriologically derived techniques which are taught by Webster et al., Kroll et al. and Walter et al.

CONCLUSION

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Pablo S. Whaley

Patent Examiner
Art Unit 1631
Office: 571-272-4425

MARJORIE A. MORAN
PRIMARY EXAMINER

Marjorie A. Moran
7/13/06